AGILENT TECHNOLOGIES, INC.
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OIPE IAP63 OCT 0 6 2008 PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): Jayati Ghosh et al.

Serial No.: 10/763,645 **Examiner:** ABDI, Amara

Filing Date: January 22, 2004 **Group Art Unit:** 2609

Title: Classification of pixels in a mocroarray image based on pixel intensities and a preview mode facilitated by pixel-intensity-based pixel classification

COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria VA 22313-1450

TRANSMITTAL OF APPEAL BRIEF

Sir:

Transmitted herewith is the Appeal Brief in this application with respect to the Notice of Appeal filed on August 4, 2008 .

The fee for filing this Appeal Brief is (37 CFR 1.17(c)) **$500.00**.

(complete (a) or (b) as applicable)

The proceedings herein are for a patent application and the provisions of 37 CFR 1.136(a) apply.

☐ (a) Applicant petitions for an extension of time under 37 CFR 1.136 (fees: 37 CFR 1.17(a)(1)-(5)) for the total number of months checked below:

☐	one month	$ 120.00
☐	two months	$ 450.00
☐	three months	$1020.00
☐	four months	$1590.00

☐ The extension fee has already been filled in this application.

☒ (b) Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

Please charge to Deposit Account **50-1078** the sum of $510.00. At any time during the pendency of this application, please charge any fees required or credit any overpayment to Deposit Account **50-1078** pursuant to 37 CFR 1.25.

A duplicate copy of this transmittal letter is enclosed.

☒ I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Date of Deposit: Oct. 2, 2008 OR

☐ I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.

Date of Facsimile:

Typed Name: Joanne Bourguignon

Signature: Joanne Bourguignon

Respectfully submitted,

Jayati Ghosh et al.

By Robert W. Bergstrom

Robert W. Bergstrom
Attorney/Agent for Applicant(s)

Reg. No. 39,906

Date: Oct. 2, 2008

Telephone No. 206.621.1933

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Respectfully submitted,

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By Robert W. Bergstrom

Robert W. Bergstrom
Attorney/Agent for Applicant(s)

Reg. No. 39,906

Date: Oct. 2, 2008

Telephone No. 206.621.1933

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

Applicants	:	Jayati Ghosh et al.
Application No.	:	10/763,645
Filed	:	January 22, 2004
For	:	Classification of pixels in a microarray image based on pixel intensities and a preview mode facilitated by pixel-intensity-based pixel classification

Examiner	:	ABDI, Amara
Art Unit	:	2609
Docket No.	:	10030722-1
Date	:	October 2, 2008

APPEAL BRIEF

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Alexandria, VA 22313-1450

Sir:

This appeal is from the decision of the Examiner, in an Office Action mailed May 2, 2008, finally rejecting claims 1-9, 11, and 14-20.

REAL PARTY IN INTEREST

Agilent Technologies is the Assignee of the present patent application. Agilent Technologies, Inc., is a Delaware corporation with headquarters in Santa Clara, CA.

RELATED APPEALS AND INTERFERENCES

Applicant's representative has not identified, and does not know of, any other appeals of interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

STATUS OF CLAIMS

Claims 1-9, 11, and 14-20 are pending in the application. Claims 1-9, 11, and 14-20 were finally rejected in the Office Action dated May 2, 2008. Applicants' appeal the final rejection of claims 1-9, 11, and 14-20 which are copied in the attached CLAIMS APPENDIX.

STATUS OF AMENDMENTS

No Amendment After Final is enclosed with this brief. The last Amendment was filed February 2, 2008.

SUMMARY OF CLAIMED SUBJECT MATTER

Independent Claim 1

Claim 1 is directed to a method for classifying pixels of a microarray image (Figures 8A-E) with observed intensities within a region of interest, the method comprising: (1) initially classifying pixels in the region of interest (1002 in Figure 10) as either feature pixels (1302) or background pixels (1204) based on the intensities of the pixels (1102 in Figure 11; lines 10 of page 16 to line 14 of page 19 and Figure 9); and (2) iteratively computing (line 15 page 19 to line 26 of page 21), for pixels within the region of interest, probabilities that the pixels are feature pixels and probabilities that the pixels are background pixels, based on pixel locations and intensities, and accordingly classifying the pixels as either feature pixels or background pixels (Figure 14).

Dependent Claims 2-9 and 11

Claim 2 is directed to the method of claim 1 wherein a feature-pixel and background-pixel classification is stored in a feature mask (1102 in Figure 11; lines 10 of page 16 to line 14 of page 19 and Figure 9). Claim 3 is directed to the method of claim 2 wherein the feature mask includes binary values corresponding to pixels in the region of interest (1002 in Figure 10), a first binary value indicating that a corresponding pixel is a feature pixel and a second binary value indicating that a corresponding pixel is a background pixel. Claim 4 is directed to the method of claim 1 wherein classifying pixels in the region of interest (1002 in Figure 10) as either feature pixels or background pixels based on the observed intensities of the pixels further includes (1102 in Figure 11; lines 10 of page 16 to

line 14 of page 19 and Figure 9): (1) determining a high pixel intensity and a low pixel intensity for the region of interest; (2) determining an intermediate point between the high pixel intensity and a low pixel intensity; (3) classifying pixels with observed pixel intensities greater than or equal to the intermediate point as feature pixels and classifying pixels with observed pixel intensities less than the intermediate point as background pixels; and (4) iteratively reclassifying pixels based on an intermediate intensity between the mean intensity of feature pixels and the mean intensity of background pixels. Claim 5 is directed to the method of claim 1 further including (1102 in Figure 11; lines 10 of page 16 to line 14 of page 19 and Figure 9) identifying hole pixels that are feature pixels surrounded by background pixels and background pixels surrounded by feature pixels and reclassifying hole pixels in order to increase continuity of feature-pixel and background-pixel classification with respect to location within the region of interest (1002 in Figure 10). Claim 6 is directed to the method of claim 1 wherein iteratively computing (line 15 page 19 to line 26 of page 21), for pixels within the region of interest (1002 in Figure 10), probabilities that the pixels are feature pixels and probabilities that the pixels are background pixels, based on pixel locations and intensities, and accordingly classifying the pixels as either feature pixels or background pixels further includes: iteratively (1) computing intensity-based outlier feature-pixel statistics and outlier background-pixel statistics; and (2) from the most recently computed intensity-based feature-pixel statistics and background-pixel statistics, determining, for each pixel, a Bayesian posterior probability P(F/i,x) that the pixel is a feature pixel and a Bayesian posterior probability P(B/i,x) that the pixel is a background pixel and classifying the pixel as a feature pixel when P(F/i,x) >= P(B/i,x) until either a maximum number of iterations are performed or until fewer than a threshold number of pixels are reclassified from feature-pixel to background-pixel and from background-pixel to feature-pixel status in the most recently executed iteration. Claim 7 is directed to the method of claim 6 wherein the Bayesian posterior probability P(F/i,x) is calculated as

$$P(F/i,x)=\frac{P(F,i,x)}{P(i,x)}=\frac{P(i/x,F)P(F,x)}{P(i,x)}=\frac{P(i/x,F)P(F/x)P(x)}{P(i,x)}$$

wherein the Bayesian posterior probability P(B/i,x) is calculated as

$$P(B/i,x)=\frac{P(B,i,x)}{P(i,x)}=\frac{P(i/x,B)P(B,x)}{P(i,x)}=\frac{P(i/x,B)P(B/x)P(x)}{P(i,x)};$$

and wherein a pixel is classified as a feature pixel when

$\frac{P(F/i,x)}{P(B/i,x)} >= 1$ (line 15 page 19 to line 26 of page 21). Claim 8 is directed to the method of claim 7 wherein Bayesian posterior probabilities P(F/i,x) and P(B/i,x) are calculated for each channel of a two-channel microarray (line 15 page 19 to line 26 of page 21), and a joint probability distribution function for two channels is then computed, which is then used for classifying pixels as feature pixels or background pixels. Claim 9 is directed to the computer-readable medium encoded with computer-executable instructions that implement the method of claim 1. Claim 11 is directed to the computer-readable medium encoded with computer-executable instructions that implement a feature extraction program (Figures 18 and 19; line 14 of page 23 to line 23 of page 24) that includes a feature-location-and-size determination step that includes the method for classifying pixels with observed intensities within the region of interest of claim 1.

Independent Claim 14

Claim 14 is directed to a feature-extraction system (Figures 18 and 19; line 14 of page 23 to line 23 of page 24) comprising: (1) a means for receiving and storing a scanned image of a microarray (Figures 8A-E; lines 16-18 of page 23)); (2) a gridding means (lines 17-18 of page 23) for determining putative feature positions and sizes within the scanned image of the microarray; (3) feature-mask-generating logic (lines 10 of page 16 to line 14 of page 19 and Figure 9) that classifies pixels as feature-pixels and background-pixels based on pixel locations and intensities; (4) preview-mode display logic (lines 6-8 of page 24) that displays feature positions and sizes obtained from the generated feature mask, solicits feedback from a user, and corrects the feature positions and sizes; and (5) a feature extraction module (lines 1-22 of page 24) that extracts signal data from the scanned image of the microarray following user acceptance of initial feature locations and sizes displayed in preview mode.

Dependent Claims 15-20

Claim 15 is directed to the feature-extraction system of claim 14 wherein the feature-mask-generating logic (1102 in Figure 11; lines 10 of page 16 to line 14 of page 19 and Figure 9) classifies pixels as feature-pixels and background-pixels based on pixel locations and intensities by: (1) initially classifying pixels in a region of interest (1002 in Figure 10) as either feature pixels or background pixels based on the intensities of the pixels;

and (2) iteratively computing, for pixels within the region of interest, probabilities that the pixels are feature pixels and probabilities that the pixels are background pixels, based on pixel locations and intensities, and accordingly classifying the pixels as either feature pixels or background pixels. Claim 16 is directed to the feature-extraction system of claim 15 wherein a feature-pixel and background-pixel classification is stored in a feature mask (1102 in Figure 11; lines 10 of page 16 to line 14 of page 19 and Figure 9). Claim 17 is directed to the feature-extraction system of claim 15 wherein classifying pixels in the region of interest (1002 in Figure 10) as either feature pixels or background pixels based on the observed intensities of the pixels further includes (1102 in Figure 11; lines 10 of page 16 to line 14 of page 19 and Figure 9): (1) determining a high pixel intensity and a low pixel intensity for the region of interest; (2) determining an intermediate point between the high pixel intensity and a low pixel intensity; (3) classifying pixels with observed pixel intensities greater than or equal to the intermediate point as feature pixels and classifying pixels with observed pixel intensities less than the intermediate point as background pixels; and (4) iteratively reclassifying pixels based on an intermediate intensity between the mean intensity of feature pixels and the mean intensity of background pixels. Claim 18 is directed to the feature-extraction system of claim 15 wherein iteratively computing (line 15 page 19 to line 26 of page 21), for pixels within the region of interest (1002 in Figure 10), probabilities that the pixels are feature pixels and probabilities that the pixels are background pixels, based on pixel locations and intensities, and accordingly classifying the pixels as either feature pixels or background pixels further includes: iteratively (1) computing intensity-based outlier feature-pixel statistics and outlier background-pixel statistics; and (2) from the most recently computed intensity-based feature-pixel statistics and background-pixel statistics, determining, for each pixel, a Bayesian posterior probability P(F/i,x) that the pixel is a feature pixel and a Bayesian posterior probability P(B/i,x) that the pixel is a background pixel and classifying the pixel as a feature pixel when P(F/i,x) >= P(B/i,x); until either a maximum number of iterations are performed or until fewer than a threshold number of pixels are reclassified from feature-pixel to background-pixel and from background-pixel to feature-pixel status in the most recently executed iteration. Claim 19 is directed to the feature-extraction system of claim 18 wherein the Bayesian posterior probability P(F/i,x) is calculated as

$$P(F/i,x) = \frac{P(F,i,x)}{P(i,x)} = \frac{P(i/x,F)P(F,x)}{P(i,x)} = \frac{P(i/x,F)P(F/x)P(x)}{P(i,x)};$$

wherein the Bayesian posterior probability P(B/i,x) is calculated as

$$P(B/i,x)=\frac{P(B,i,x)}{P(i,x)}=\frac{P(i/x,B)P(B,x)}{P(i,x)}=\frac{P(i/x,B)P(B/x)P(x)}{P(i,x)};$$

and wherein a pixel is classified as a feature pixel when

(line 15 page 19 to line 26 of page 21) $\frac{P(F/i,x)}{P(B/i,x)}>=1$. Claim 20 is directed to the feature-extraction system of claim 19 wherein Bayesian posterior probabilities P(F/i,x) and P(B/i,x) are calculated for each channel of a two-channel microarray, and a joint probability distribution function for two channels is then computed, which is then used for classifying pixels as feature pixels or background pixels (line 15 page 19 to line 26 of page 21).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. The rejection of claims 1-20 under 35 U.S.C. §103(a) as being unpatentable over Yakhini et al., EP 1 162 572 A2 ("Yakhini") and various combinations of other references, primarily including Mittal et al., U.S. Patent Application Publication No. 2005/0286764 A1 ("Mittal").

ARGUMENT

Claims 1-20 are pending in the current application. In an office action dated May 2, 2008 ("Office Action"), the Examiner finally rejected claims 1-4 under 35 U.S.C. §103(a) as being unpatentable over Lim, U.S. Patent Application Publication No. 2004/0017579 ("Lim") in view of Mittal et al., U.S. Patent Application Publication No. 2005/0286764 ("Mittal"), rejected claim 5 under 35 U.S.C. §103(a) as being unpatentable over Lim and Mittal in further view of Lee et al., U.S. Patent Application Publication No. 2004/0202368 ("Lee"), rejected claims 6-7 under 35 U.S.C. §103(a) as being unpatentable over Lim and Mittal in further view of Bow et al., (STIC), pattern recognition and image processing ("Bow"), rejected claim 8 under 35 U.S.C. §103(a) as being unpatentable over Lim, Mittal, Bow, and in further view of Padilla et al., U.S. Patent Application Publication No. 2003/0233197 ("Padilla"), rejected claims 9 and 11 under 35 U.S.C. §103(a) as being unpatentable over Lim and Mittal in further view of Gelenbe et al., U.S. Patent No. 5,995,651 ("Gelenbe"), rejected claim 10 under 35 U.S.C. §103(a) as being unpatentable over Lim and

Mittal in further view of Kondo, U.S. Patent Application Publication No. 2004/0234160 ("Kondo"), rejected claims 12 and 13 under 35 U.S.C. §103(a) as being unpatentable over Lim, Mittal, and Gelenbe in further view of Belkin et al, U.S. Patent No. 6,738,087 ("Belkin"), rejected claim 14 under 35 U.S.C. §103(a) as being unpatentable over Mittal in view of Kamitani et al., U.S. Patent No. 6,327,385 ("Kamitani"), rejected claims 15-17 under 35 U.S.C. §103(a) as being unpatentable over Mittal and Kamitani and in further view of Lim, rejected claims 18-19 under 35 U.S.C. §103(a) as being unpatentable over Mittal, Kamitani, and Lim, in further view of Bow, and rejected claim 20 under 35 U.S.C. §103(a) as being unpatentable over Mittal, Kamitani, Lim, Bow, and in further view of Padilla. Applicants respectfully traverse these rejections.

ISSUE 1

1. The rejection of claims 1-20 under 35 U.S.C. §103(a) as being unpatentable over Yakhini et al., EP 1 162 572 A2 ("Yakhini") and various combinations of other references, primarily including Mittal et al., U.S. Patent Application Publication No. 2005/0286764 A1 ("Mittal").

In the Office Action, the Examiner separately rejects many small groups of claims under various different combinations of cited references. However, every rejection cites Yakhini, and the rejections of all but one claim, claim 14, rely on both Yakhini and Mittal. Therefore, in the interest of brevity, Applicants address these two references, to show that neither reference teaches, mentions, or suggests that for which it is cited. Because all of the rejections depend primarily on these two references, a showing that neither reference is relevant to the currently claimed invention demonstrates, in Applicants' representative's respectfully offered opinion, that none of the 35 U.S.C. §103(a) rejections is well founded and that none meets the requirements for a *prima facie* obviousness-type rejection.

As discussed in the first sentence of the background-of-the-invention section of the current application, beginning on line 11 of page 1: "The present invention is related to methods and systems for determining which pixels, in a digital image of a microarray, are associated with features of the microarray, and which pixels are background pixels associated with inter-feature regions of a microarray." The current application provides a very lengthy and detailed discussion of microarrays, microarray features, background pixels, and inter-feature regions. This discussion begins on line 19 of page 1 and continues to line 30 of page

6, and then resumes on line 11 of page 9 and continues through line 22 of page 15. A microarray is a manufactured product that comprises a substrate onto which features are arranged in a regular two-dimensional grid or lattice. Each feature contains a different type of probe molecule, generally oligonucleotides. Figures 4-7 of the current application illustrate the general concept of a microarray.

Microarrays are scanned, by microarray scanners, to produce digitally encoded images of the surface of the microarray. Target molecules bound to probe molecules of different features emit light or other types of radiation that can be imaged to produce raw data, such as a portion of a microarray image shown in Figure 8A of the current application. Figure 8A of the current application, as discussed in the current application beginning on line 31 of page 13, shows a 25 x 25 pixel region of a digital image of a microarray. "Each two-digit number in the two-dimensional array of numbers in Figure 8A, such as the two-digit number '02' 802, represents the intensity associated with the pixel." Figure 8B of the current application shows the approximately elliptical line boundaries of two elliptical-disk-like regions within the portion of the microarray image shown in Figure 8B. These elliptical line boundaries can be thought of as contour lines, such as the contour lines on a topographical map, which show the boundaries between regions with different average intensities. Outside of the larger, disk-shaped region bounded by roughly elliptical line 812, referred to in Figure 8B as region 814, pixel intensities are relatively low, with an average intensity value, by inspection, somewhere between 8 and 11. The region bounded by the roughly elliptical line 810 and the roughly elliptical line 812 is an intermediate-intensity region in which pixel intensities have an average value, by inspection, of somewhere between 2400 and 2500 (note the two-digit numbers in Figures8A-E refer to 100's of counts, or other signal-intensity units). The innermost region, bounded by the roughly elliptical line 810, contains pixels having high-intensity values with an average value, by inspection, of between 4900 and 5000. These regions, shown in Figure 8B, comprise an ideal image of a single feature of a microarray. The region outside of the roughly elliptical line 812, referred to as 814 in Figure 8B, constitutes a background region, or an inter-feature region.

In many cases, the signals produced by microarray features and image of a microarray are not so well differentiated from background, so that it is difficult to determine which portion of the image corresponds to background and which portion corresponds to a region of interest corresponding to a microarray feature. Figures 8C-E illustrate portions of microarray images encompassing a feature that cannot be so easily visually distinguished as

in the case of Figures 8A-B. As discussed beginning on line 21 of page 16 of the current application, Figure 10 shows a portion of a microarray image clearly containing the image of a feature 1004, but also containing two other relatively high-intensity regions 1008 and 1010. As discussed in the current application beginning on line 31 of page 16:

> It is a goal of feature-mask generation to accurately identify those pixels within the pixel-based ROI intensity data set that correspond to the image of a feature and to mask out high-intensity pixels, such as those in regions 1008 and 1010 in Figure 10, that do not correspond to feature pixels. In addition, there may be various, isolated intensity-outlying pixels, both in the background and feature regions of an ROI, that also need to be identified and taken into consideration during signal extraction from pixel-intensity data.

The approach to distinguishing feature pixels from background pixels within a region of interest is described in the current application beginning on line 23 of page 15, with reference to Figures 9-19. A preliminary feature mask, shown in Figure 11, is generated from the region of interest by partitioning pixels of the region of interest between candidate feature pixels, represented by Boolean value "1," and candidate background pixels, represented by Boolean value "0." Note that the three high-intensity regions discussed with reference to Figure 10 appear in Figure 11 as regions largely containing Boolean value "1." Employing various operations, a final feature mask, shown in Figure 14, is produced in which the feature pixels are identified by Boolean value "1" and the non-feature, background pixels are identified by Boolean value "0." Details of the methods by which this final feature mask are generated can be found in the detailed description of the current application.

As has been repeatedly pointed out to the Examiner, Mittal is completely unrelated to anything in the current application or anything to which the current claims are directed. Mittal describes a method for modeling dynamic scenes in video images, where dynamic scenes are scenes in which objects move. Mittal detects motion by comparing frames close to one another within a sequence of frames that represent the video image. Mittal clearly discusses this beginning with paragraph [0010] on page 1 of Mittal's published patent application. Mittal attempts to develop predictive models to predict current input based on past observations by modeling a visual scene captured in a video image as a time series. Also, Mittal attempts to develop a method for classifying observations based on video images as related to the foreground of a scene versus the background of a scene. The foreground and background refer to, as discussed in paragraphs [0012-0014], a further-off, relatively static portion of a video image or scene captured by a video image, in the case of

background, and closer, moving objects that move with respect to the background, in the case of the foreground portion of a scene captured in a video image.

The word "background" used in Mittal has nothing whatsoever to do with the background pixels of the image of a microarray. Those even cursorily familiar with microarray-data processing, video images, computer science, photography, and many other fields recognize that the word "background" used with reference to photography, scenes, and video images is quite unrelated to the word "background" used in reference to inter-feature regions of the image of a microarray. In Mittal, the background is a relatively motionless portion of a scene, and is defined in terms of motion discerned from comparing different frames within a sequence of frames that represent a portion of a video image. By contrast, the background pixels in the image of a microarray refer to those pixels with generally relatively low intensity that occur in the non-feature-portions of the image of a microarray. Those familiar with microarrays and microarray scanning understand that the entire surface of a microarray, including both the features and inter-feature regions, are part of the single rigid substrate, and do not move relative to one another. By contrast, in Mittal, portions of the scene referred to as background are differentiated between portions of the scene referred to as foreground by relative motion. In photography, the background of a scene is generally further from the camera than the foreground, and needs a different focus than that used for foreground objects. By contrast, those familiar with microarray scanning realize that both the feature pixels and background pixels in the image of a microarray occur in a single, fixed plane on the surface of a rigid substrate, and thus do not differ in distance from a lens, or depth in a real scene.

Processing of video images using motion information obtained by comparing frames within a sequence of frames is absolutely and completely unrelated to interpretation of pixels within the image of a microarray generated by a microarray scanner. In Applicants' representative's respectfully offered opinion, Mittal should not have been cited in the current case. Of course, Mittal does not once teach, mention, or suggest anything related to microarrays, features, inter-feature regions, regions of interest, or anything else related to, or mentioned in, the current claims.

By contrast, the Yakhini reference is related to processing of microarray data. In fact, Applicants' representative drafted both Yakhini as well as the current application. Yakhini is not directed, however, to the subject matter to which the current application and current claims are directed, namely, classifying pixels within the region of interest of a

microarray image as background pixels or feature pixels.

The Examiner refers to Figure 2, paragraph [0004], lines 7-20, of Yakhini as clearly teaching the classifying of pixels as either feature pixels or background pixels. However, Figure 2 of Yakhini, as explicitly stated by Yakhini, "illustrates the two-dimensional grid of pixels in a square area of a scanned image encompassing feature 101 of Figure 1." In other words, Figure 2 of Yakhini is essentially identical to Figure 8A of the current application in that it shows a small region of a scanned image of a microarray. Figure 2 shows the pixel intensities within a scanned image of a microarray included in and surrounding a feature. The rest of paragraph [0004] of Yakhini describes characteristics of images of microarrays, including the fact that features generally have higher intensity values than background regions, but that intensity pixels within background regions may arise due to surface contaminants and other problems. There is nothing in Figure 2 or paragraph [0004] of Yakhini that teaches, mentions, or even remotely suggests any type of method for classifying the pixels as being feature pixels or background pixels. The fact that a reader can pick out high-intensity regions in Figure 2 of Yakhini and in Figure 8A of the current application is completely beside the point. In fact, the current application notes that, in certain ideal cases, such as that depicted in Figure 8A of the current application and Figure 2 of Yakhini, feature pixels can be relatively correctly distinguished from background pixels by visual examination of the pixel intensities. However, in non-ideal cases, differentiation of background pixels from feature pixels is difficult. Figure 2 of Yakhini and Figure 8A of the current application show ideal cases. The fact that, for ideal cases, feature pixels can be distinguished from background pixels by visual inspection has nothing whatsoever to do with the currently claimed methods of computationally classifying pixels as background pixels or feature pixels.

Claim 1 of the current claim set, as one example, includes a step of initially classifying pixels as feature pixels or background pixels based on pixel intensities, and a second step of iteratively computing probabilities that pixels are feature pixels and probabilities that pixels are background pixels based on pixel locations and intensities in order to classify pixels as feature pixels or background pixels. Nothing in paragraph [0004] of Yakhini suggests an initial classification step or a subsequent iterative step of computing probabilities that pixels are feature pixels or background pixels and refining the classification based on those probabilities. Even by simply comparing terms and phrases of the current claims with those in Yakhini, it is absolutely and unambiguously clear that paragraph [0004]

of Yakhini is a descriptive passage that describes an ideal portion of an image of a microarray, and does not once teach, mention, or suggest any kind of classification, iterative computing, or probabilities related to whether or not pixels are feature pixels or background pixels. Citation of Figure 2 in paragraph [0004] of Yakhini makes no sense. In fact, as previously pointed out to the Examiner, Yakhini, as discussed in paragraph [0001] of Yakhini, is concerned with determining the orientation of a microarray image in order to construct an abstract grid by which to index each of the features within the microarray image. Yakhini does not teach, mention, or suggest any method, or even a need for a method, to classify pixels within a region of interest as feature pixels or background pixels. Yakhini does, in subsequent sections, discuss a blob-analysis technique for computing the highest-intensity areas within the image of a microarray in order to compute refined coordinates for the centers of disk-shaped inner regions of interest. However, this technique is based on intensity thresholding, and is concerned only with computing coordinates responding to highest-intensity regions, and is not in any way directed to classifying pixels as background pixels or foreground pixels.

As can be seen by the detailed summary of the Examiner's rejections, all of the Examiner's rejections, with the exception of the rejection of claim 14, rely primarily on Yakhini and Mittal. As discussed above, neither Yakhini nor Mittal are in any way related to classification of pixels as foreground pixels and background pixels within regions of interest in the image of a microarray. The rejection of claim 14 is based primarily on Yakhini, and is therefore as unfounded as the rejections of the other claims. Although the standards for obviousness-type rejections have changed somewhat under the recent *KSR* decision, it is still the case that an examiner must find clear teachings and/or suggestions of the elements of a claim within the cited references and within the knowledge of those skilled in the art. Neither Yakhini nor Mittal provides any teaching, mention, or suggestion of the currently claimed method and system. Mittal is utterly and completely unrelated to microarrays and processing of microarray data. For this reason, there is simply no basis for citation of either reference, and obviously no rational basis for a 35 U.S.C. §103(a) obviousness-type rejection based on either or both of these references.

According to M.P.E.P. §2141(III), obviousness-type rejections require rational underpinnings and logical arguments, and cannot be based on conclusory statements. Because Mittal is absolutely unrelated to the current application and claims, and because the Examiner cannot point to a single reference in Mittal to microarrays, background pixels in

inter-feature regions of the image of a microarray, computational methods for classifying pixels as belonging to features of an image of a microarray or background regions of the image of a microarray, or to anything else even remotely related to the field to which the current application and claims are directed, the Examiner's arguments for using the Mittal reference, and the rejections based on the Mittal reference, cannot be anything but conclusory. The Examiner's attempt to read claims directed to a method for classifying pixels as background pixels or feature pixels onto a descriptive paragraph that neither mentions nor suggests anything at all related to methods for making such classifications, including using probabilities and iterative methods, and other of the specific limitations of the current claims, cannot be anything but conclusory. There is simply no support in Mittal or Yakhini for what the Examiner attempts to attribute to these references.

CONCLUSION

All of the Examiner's 35 U.S.C. §103(a) obviousness-type rejections are based on Yahkini or Yahkini and Mittal. Mittal is directed to modeling motion in video images, and is completely unrelated to microarrays and analysis of scanned images of microarrays. Mitttal fails to teach, mention, or suggest any element of any of the current claims. Although Yakhini is related to microarray-image analysis, Yakhini is directed to methods for properly orienting microarray images and constructing two-dimensional grids that identify feature locations. Yakhini does not teach, mention, or suggest anything related to iterative methods for classifying pixels within a region of interest as background pixels and feature pixels based on probabilities. Neither Yakhini nor Mittal teach, mention, or suggest that for which the Examiner has cited them and, therefore, the Examiner's 35 U.S.C. §103(a) obviousness-type rejections based on Yahkini and Mittal are clearly unfounded.

Applicants respectfully submit that all statutory requirements are met and that the present application is allowable over all the references of record. Therefore, Applicants respectfully request that the present application be passed to issue.

Respectfully submitted,
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CLAIMS APPENDIX

1. A method for classifying pixels of a microarray image with observed intensities within a region of interest, the method comprising:

initially classifying pixels in the region of interest as either feature pixels or background pixels based on the intensities of the pixels; and

iteratively computing, for pixels within the region of interest, probabilities that the pixels are feature pixels and probabilities that the pixels are background pixels, based on pixel locations and intensities, and accordingly classifying the pixels as either feature pixels or background pixels.

2. The method of claim 1 wherein a feature-pixel and background-pixel classification is stored in a feature mask.

3. The method of claim 2 wherein the feature mask includes binary values corresponding to pixels in the region of interest, a first binary value indicating that a corresponding pixel is a feature pixel and a second binary value indicating that a corresponding pixel is a background pixel.

4. The method of claim 1 wherein classifying pixels in the region of interest as either feature pixels or background pixels based on the observed intensities of the pixels further includes:

determining a high pixel intensity and a low pixel intensity for the region of interest;

determining an intermediate point between the high pixel intensity and a low pixel intensity;

classifying pixels with observed pixel intensities greater than or equal to the intermediate point as feature pixels and classifying pixels with observed pixel intensities less than the intermediate point as background pixels; and

iteratively reclassifying pixels based on an intermediate intensity between the mean intensity of feature pixels and the mean intensity of background pixels.

5. The method of claim 1 further including identifying hole pixels that are feature pixels surrounded by background pixels and background pixels surrounded by feature pixels and reclassifying hole pixels in order to increase continuity of feature-pixel and background-pixel

classification with respect to location within the region of interest.

6. The method of claim 1 wherein iteratively computing, for pixels within the region of interest, probabilities that the pixels are feature pixels and probabilities that the pixels are background pixels, based on pixel locations and intensities, and accordingly classifying the pixels as either feature pixels or background pixels further includes:

iteratively

computing intensity-based outlier feature-pixel statistics and outlier background-pixel statistics;

from the most recently computed intensity-based feature-pixel statistics and background-pixel statistics, determining, for each pixel, a Bayesian posterior probability P(F/i,x) that the pixel is a feature pixel and a Bayesian posterior probability P(B/i,x) that the pixel is a background pixel and classifying the pixel as a feature pixel when P(F/i,x) >= P(B/i,x);

until either a maximum number of iterations are performed or until fewer than a threshold number of pixels are reclassified from feature-pixel to background-pixel and from background-pixel to feature-pixel status in the most recently executed iteration.

7. The method of claim 6

wherein the Bayesian posterior probability P(F/i,x) is calculated as

$$P(F/i,x)=\frac{P(F,i,x)}{P(i,x)}=\frac{P(i/x,F)P(F,x)}{P(i,x)}=\frac{P(i/x,F)P(F/x)P(x)}{P(i,x)};$$

wherein the Bayesian posterior probability P(B/i,x) is calculated as

$$P(B/i,x)=\frac{P(B,i,x)}{P(i,x)}=\frac{P(i/x,B)P(B,x)}{P(i,x)}=\frac{P(i/x,B)P(B/x)P(x)}{P(i,x)};$$

and wherein a pixel is classified as a feature pixel when

$$\frac{P(F/i,x)}{P(B/i,x)}>=1.$$

8. The method of claim 7 wherein Bayesian posterior probabilities P(F/i,x) and P(B/i,x) are calculated for each channel of a two-channel microarray, and a joint probability distribution function for two channels is then computed, which is then used for classifying pixels as feature pixels or background pixels.

9. A computer-readable medium encoded with computer-executable instructions that implement the method of claim 1.

10. Cancel

11. A computer-readable medium encoded with computer-executable instructions that implement a feature extraction program that includes a feature-location-and-size determination step that includes the method for classifying pixels with observed intensities within the region of interest of claim 1.

12-13. Cancel

14. A feature-extraction system comprising:

a means for receiving and storing a scanned image of a microarray;

a gridding means for determining putative feature positions and sizes within the scanned image of the microarray;

feature-mask-generating logic that classifies pixels as feature-pixels and background-pixels based on pixel locations and intensities;

preview-mode display logic that displays feature positions and sizes obtained from the generated feature mask, solicits feedback from a user, and corrects the feature positions and sizes; and

a feature extraction module that extracts signal data from the scanned image of the microarray following user acceptance of initial feature locations and sizes displayed in preview mode.

15. The feature-extraction system of claim 14 wherein the feature-mask-generating logic classifies pixels as feature-pixels and background-pixels based on pixel locations and intensities by:

initially classifying pixels in a region of interest as either feature pixels or background pixels based on the intensities of the pixels; and

iteratively computing, for pixels within the region of interest, probabilities that the pixels are feature pixels and probabilities that the pixels are background pixels, based on

pixel locations and intensities, and accordingly classifying the pixels as either feature pixels or background pixels.

16. The feature-extraction system of claim 15 wherein a feature-pixel and background-pixel classification is stored in a feature mask.

17. The feature-extraction system of claim 15 wherein classifying pixels in the region of interest as either feature pixels or background pixels based on the observed intensities of the pixels further includes:

determining a high pixel intensity and a low pixel intensity for the region of interest;

determining an intermediate point between the high pixel intensity and a low pixel intensity;

classifying pixels with observed pixel intensities greater than or equal to the intermediate point as feature pixels and classifying pixels with observed pixel intensities less than the intermediate point as background pixels; and

iteratively reclassifying pixels based on an intermediate intensity between the mean intensity of feature pixels and the mean intensity of background pixels.

18. The feature-extraction system of claim 15 wherein iteratively computing, for pixels within the region of interest, probabilities that the pixels are feature pixels and probabilities that the pixels are background pixels, based on pixel locations and intensities, and accordingly classifying the pixels as either feature pixels or background pixels further includes:

iteratively

computing intensity-based outlier feature-pixel statistics and outlier background-pixel statistics;

from the most recently computed intensity-based feature-pixel statistics and background-pixel statistics, determining, for each pixel, a Bayesian posterior probability $P(F/i,x)$ that the pixel is a feature pixel and a Bayesian posterior probability $P(B/i,x)$ that the pixel is a background pixel and classifying the pixel as a feature pixel when $P(F/i,x) >= P(B/i,x)$;

until either a maximum number of iterations are performed or until fewer than a threshold number of pixels are reclassified from feature-pixel to background-pixel and from

background-pixel to feature-pixel status in the most recently executed iteration.

19. The feature-extraction system of claim 18

wherein the Bayesian posterior probability P(F/i,x) is calculated as

$$P(F/i,x) = \frac{P(F,i,x)}{P(i,x)} = \frac{P(i/x,F)P(F,x)}{P(i,x)} = \frac{P(i/x,F)P(F/x)P(x)}{P(i,x)};$$

wherein the Bayesian posterior probability P(B/i,x) is calculated as

$$P(B/i,x) = \frac{P(B,i,x)}{P(i,x)} = \frac{P(i/x,B)P(B,x)}{P(i,x)} = \frac{P(i/x,B)P(B/x)P(x)}{P(i,x)};$$

and wherein a pixel is classified as a feature pixel when

$$\frac{P(F/i,x)}{P(B/i,x)} >= 1.$$

20. The feature-extraction system of claim 19 wherein Bayesian posterior probabilities P(F/i,x) and P(B/i,x) are calculated for each channel of a two-channel microarray, and a joint probability distribution function for two channels is then computed, which is then used for classifying pixels as feature pixels or background pixels.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.